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14. ABSTRACT These experiments demonstrated that (1) intrathecal N/OFQ did not produced hyperalgesia-like effects as reported in rodents, (2) systemic Ro 64-6198 produced antinociceptive effects that are independent from mu opioid receptors, and (3) activation of NOP receptors produced antinociception without reinforcing/abuse liability in monkeys. Ro 64-6198 has only been studied in rodent species. This is the first functional study to investigate the behavioral effects of Ro 64-6198 in primates. More importantly, Ro 64-6198 produces antinociception like alfentanil, a commonly used mu opioid analgesic in the clinic, in two primate nociceptive models, but Ro 64-6198 does not produce reinforcing effects /abuse liability like mu receptor opioid analgesics. These findings may indicate that NOP receptor agonists may be a new generation of novel analgesics without abuse liability.					
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INTRODUCTION

The studies proposed in this project will test the hypotheses that in the non-human primates (1) the functions/behavioral effects of NOP receptors are independent of classical opioid receptors, (2) activation of the NOP receptor produces strong antinociception without abuse liability, and (3) NOP receptor agonists possess a promising therapeutic profile as analgesics compared to mu opioid agonists following chronic administration.

BODY

Task 1. Extensive evaluation of the behavioral effects of intrathecally administered N/OFQ in non-human primates.

a. Study behavioral effects of ultra-low doses of intrathecal N/OFQ over a wide dose range using a warm water tail withdrawal assay and behavioral observations.

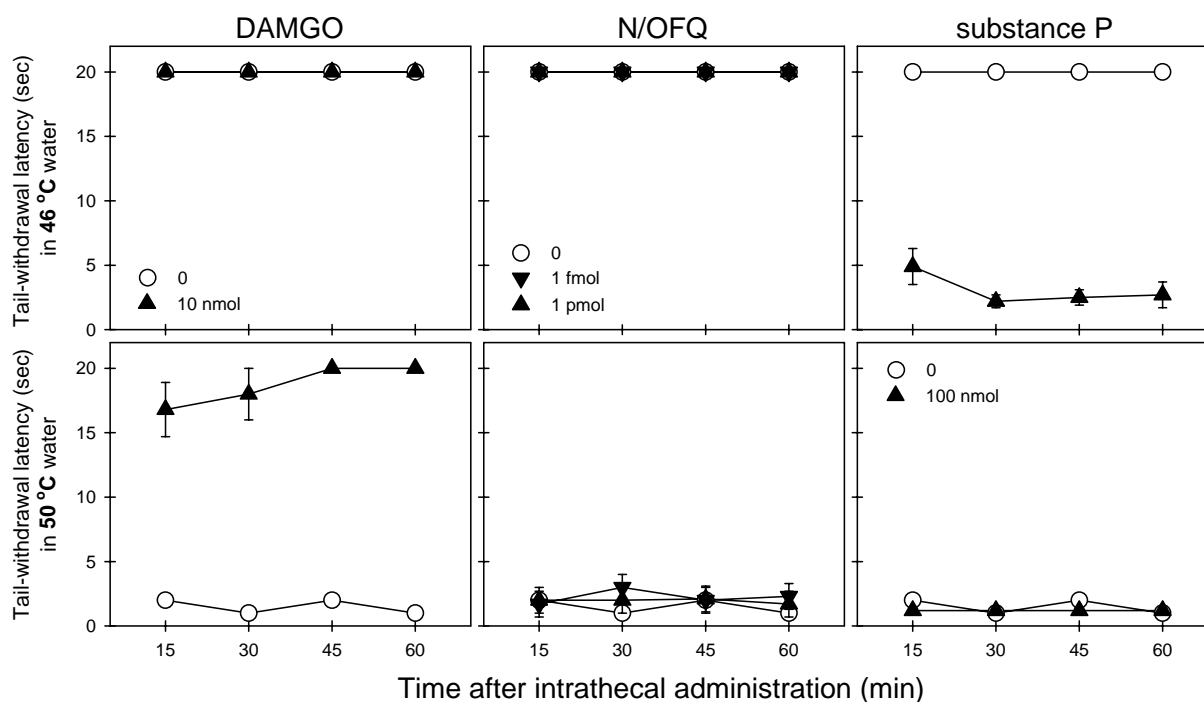


Figure 1. Effects of intrathecally administered DAMGO, N/OFQ, and substance P on the thermal nociceptive threshold of monkeys.

Figure 1 compares the effects of ultra-low doses of intrathecal N/OFQ (i.e., 1 fmol and 1 pmol) with those of a mu opioid receptor agonist, DAMGO (as an antinociceptive agent), and a neurokinin receptor agonist, substance P (as a nociceptive agent) in the same monkeys. These findings indicate that ultra-low doses of intrathecal N/OFQ did not change the monkey's thermal nociceptive threshold (Figure 1, middle panels). For comparison, intrathecal DAMGO 10 nmol produced antinociception in 50C water (Figure 1, left-bottom panel) and intrathecal substance P 100 nmol produced nociception (i.e., hyperalgesia-like responses) in 46C water (Figure 1, right-top panel).

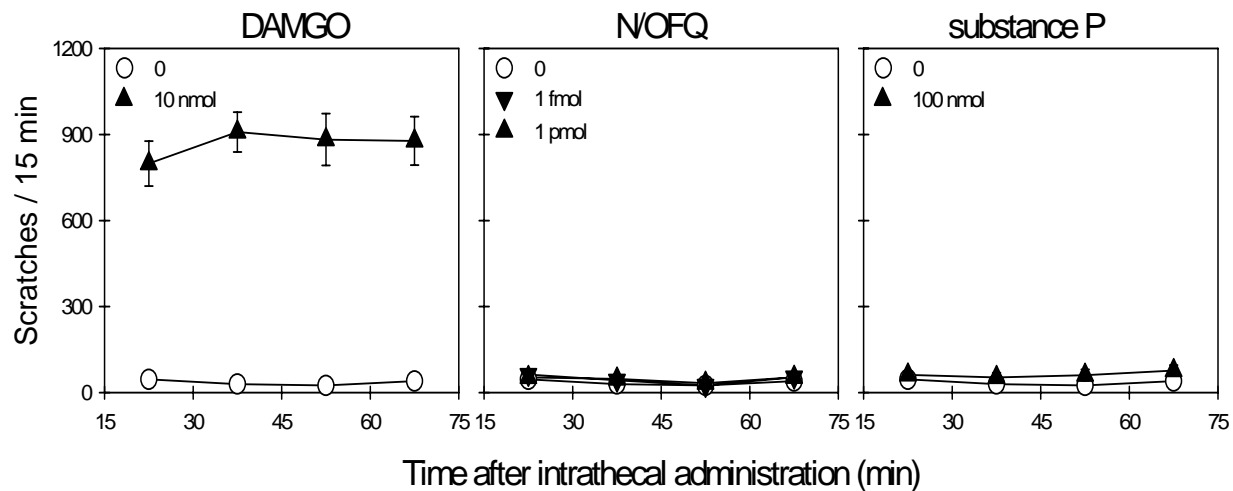


Figure 2. Effects of intrathecally administered DAMGO, N/OFQ, and substance P on behavioral responses in monkeys.

Figure 2 compares the effects of ultra-low doses of intrathecal N/OFQ (i.e., 1 fmol and 1 pmol) with those of a mu opioid receptor agonist, DAMGO, and a neurokinin receptor agonist, substance P in the same monkeys. These findings indicate that ultra-low doses of intrathecal N/OFQ did not elicit behavioral scratching responses (Figure 2, middle panel). In contrast, intrathecal DAMGO 10 nmol produced profound scratching responses (Figure 2, left panel).

Taken together, these findings indicate that ultra-low doses of intrathecal N/OFQ did not change the nociceptive threshold and it also did not elicit any observable behavioral responses. Ultra-low doses of intrathecal N/OFQ (i.e., fmol) produced pain-like behavior manifested by scratching, biting, and licking behaviors in mice (Sakurada et al., 1999). It is possible that intrathecal N/OFQ only produced antinociceptive effects in monkeys (Ko et al., 2006) and the function of NOP receptors in the spinal cord may not be the same between rodents and primates.

Task 2. Comparison of effectiveness of systemically administered Ro 64-6198 in different experimental pain models in non-human primates.

- a. Determine the doses of systemic Ro 64-6198, a non-peptidic NOP receptor-selective agonist, that produce antinociception in monkeys using a warm water 50° C tail withdrawal assay.

Task 3. Clarification of the receptor selectivity and site of actions of NOP receptor agonists by conducting receptor antagonist studies *in vivo*.

- a. Determine the *in vivo* apparent pA_2 value of J-113397, a non-peptidic NOP receptor-selective antagonist, against systemic Ro 64-6198-induced antinociception in monkeys.

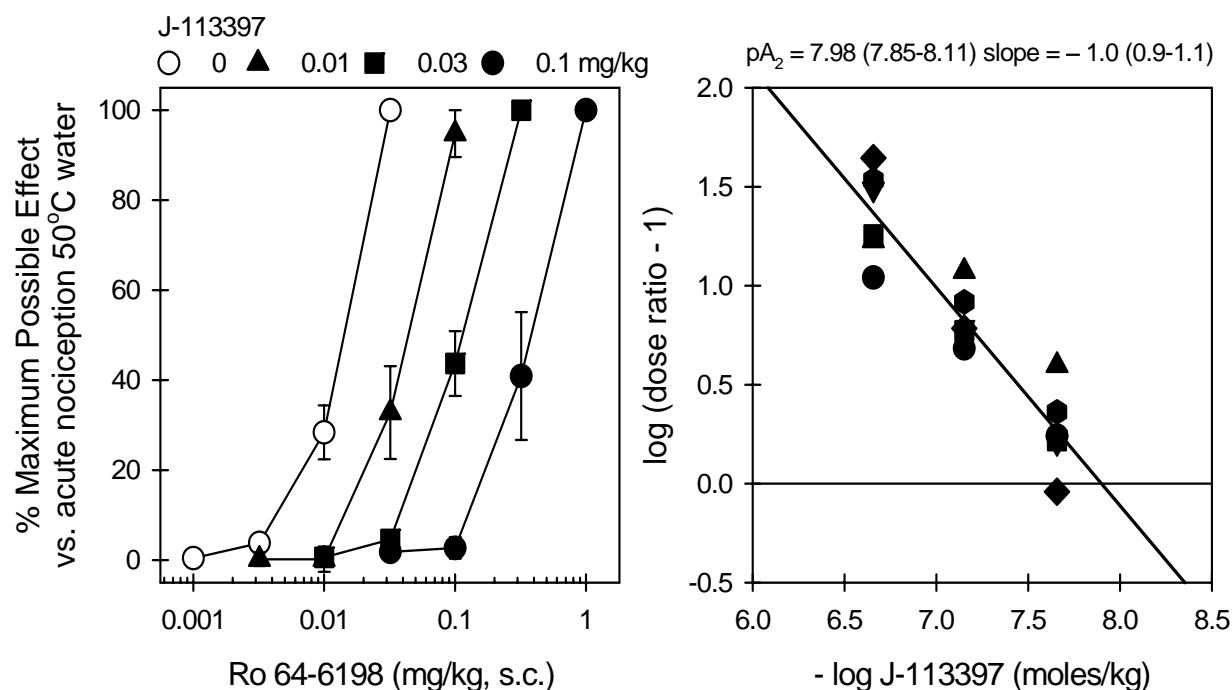


Figure 3. In vivo antagonist potency of J-113397 against Ro 64-6198-induced antinociception in monkeys. Left panel, antagonist effects of s.c. J-113397 on the dose response curve of Ro 64-6198-induced antinociception in 50°C water. Abscissa, dose of s.c. Ro 64-6198 (mg/kg). Ordinate, percentage of maximum possible effect for antinociception. Right panel, a Schild plot for J-113397. Abscissa, negative log unit for J-113397 in moles per kilogram. Ordinate, log of (dose ratio - 1). Each point was converted from individual dose ratio for each dosing condition presented in the top

panel. Closed symbols represent different subjects. The mean pA_2 value and slope of J-113397 are shown with 95% confidence limits in parentheses.

Figure 3 illustrates the antagonist effect of J-113397 against Ro 64-6198-induced antinociception in 50°C water. Mean ED50 (95% confidence limit) value of s.c. Ro 64-6198-induced antinociception with vehicle pretreatment was 0.014 (0.011-0.016) mg/kg. Pretreatment with J-113397 dose-dependently produced rightward shifts of the dose response curve of Ro 64-6198-induced antinociception. These dose-dependent antagonist effects of J-113397 were graphed in a Schild plot with values derived from individual dose ratios for each subject. The mean pA_2 value of J-113397 was 7.98 (7.85-8.11) with a slope of -1. The doses of J-113397 alone did not change the thermal threshold of monkeys (i.e., no changes in the tail withdrawal latencies in 42, 46, or 50°C water).

Task 3. Clarification of the receptor selectivity and site of actions of NOP receptor agonists by conducting receptor antagonist studies *in vivo*.

- b. Cross-examine the antagonist potency of naltrexone, an opioid receptor antagonist, on Ro 64-6198-induced antinociception and the antagonist potency of J-113397 on morphine-induced antinociception.

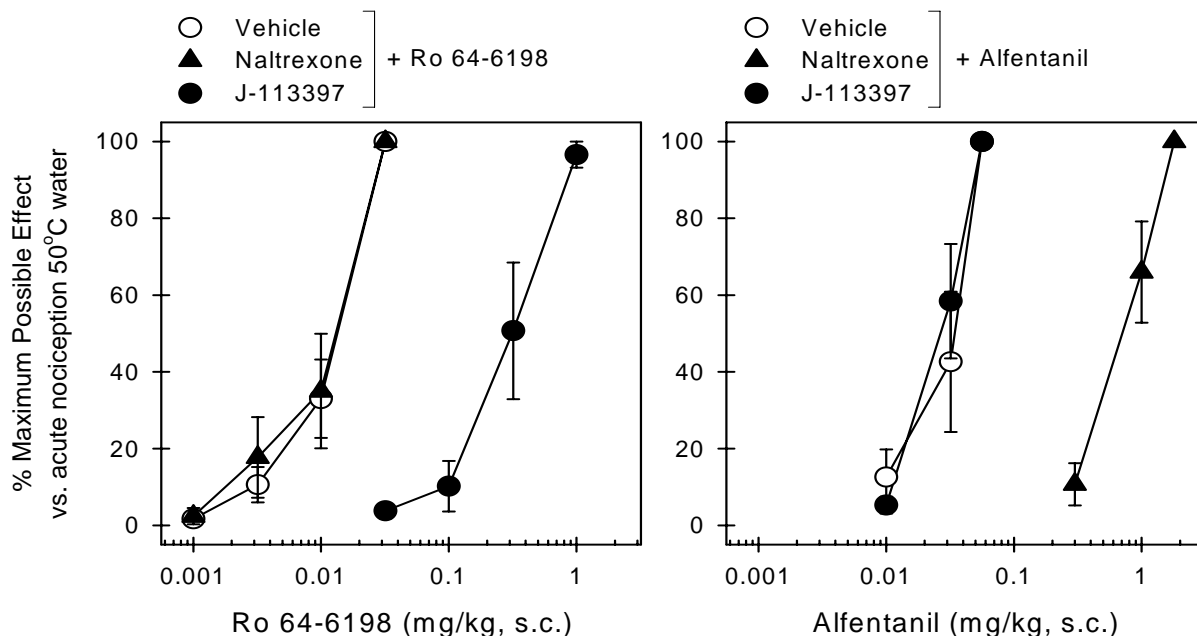


Figure 4. Effects of mu opioid receptor and NOP receptor antagonists on alfentanil- and Ro 64-6198-induced antinociceptive effects in monkeys. A mu opioid receptor antagonist (Naltrexone, 0.03 mg/kg, s.c.) or a NOP receptor antagonist (J-113397, 0.1 mg/kg, s.c.) was administered s.c. 15 min before re-determination of the dose-response curve of alfentanil and Ro 64-6198. Left panel, antagonist effects of s.c. naltrexone and J-113397 on the dose response curve of Ro 64-6198-induced antinociception in 50°C water. Right panel, antagonist effects of s.c. naltrexone and J-113397 on the dose response curve of alfentanil-induced antinociception in 50°C water. Symbols represent different dosing conditions for the same monkeys.

Figure 4 compares the antagonist effects of naltrexone and J-113397 on the antinociceptive effects produced by s.c. Ro 64-6198 and alfentanil. Left panel shows a

single dose of J-113397 0.1 mg/kg produced a large rightward shift of the dose response curve of Ro 64-6198-induced antinociception. The mean J-113397 pK_B value was 8.02 (7.78-8.26) under this condition. Naltrexone 0.03 mg/kg failed to block Ro 64-6198-induced antinociception. The ED50 value of Ro 64-6198 dose response for vehicle pretreatment (0.012 mg/kg) was similar to that for naltrexone pretreatment (0.013 mg/kg). In contrast, right panel shows a single dose of naltrexone 0.03 mg/kg produced a large rightward shift of the dose response curve of alfentanil-induced antinociception. The mean naltrexone pK_B value was 8.44 (8.18-8.70) under this condition. J-113397 0.1 mg/kg failed to block alfentanil-induced antinociception. The ED50 value of alfentanil dose response for vehicle pretreatment (0.031 mg/kg) was similar to that for J-113397 pretreatment (0.026 mg/kg).

Taken together, these findings showed that systemic Ro 64-6198 alone produced antinociceptive effects which were blocked dose-dependently by J-113397, a selective NOP receptor antagonist. *In vivo* apparent pA_2 analysis was used because this quantitative procedure offers a powerful approach to establish receptor-mediated drug effects (Arunlakshana and Schild, 1959; Tallarida et al., 1979). In the present study, J-113397 dose-dependently produced parallel rightward shifts of the dose response curve of Ro 64-6198-induced antinociception (figure 3), indicating that the agonist and antagonist compete for the same NOP receptors in a reversible manner. The pA_2 value of J-113397, 8.0, was approximately 3-fold less than the naltrexone pA_2 value of 8.5 under the same behavioral assay conditions (Ko et al., 1998a), indicating that both naltrexone and J-113397 are potent antagonists *in vivo* for mu opioid receptors and NOP receptors, respectively, in monkeys. More importantly, cross-examination of both antagonists against different agonists demonstrated that both alfentanil- and Ro 64-6198-induced antinociceptive effects were mediated by mu opioid receptors and NOP receptors, respectively (figure 4). The pK_B values of J-113397 for Ro 64-6198 and naltrexone for alfentanil were 8.0 and 8.4, respectively. Moreover, J-113397 0.1 mg/kg failed to block alfentanil-induced antinociception and naltrexone 0.03 mg/kg failed to block Ro 64-6198-induced antinociception. These results indicate that antinociceptive effects of opioid analgesics can be produced by two independent opioid receptor mechanisms in monkeys.

Task 2. Comparison of effectiveness of systemically administered Ro 64-6198 in different experimental pain models in non-human primates.

- b. Compare the antinociceptive effects of systemic Ro 64-6198 with those of systemic morphine in capsaicin-induced allodynia and carrageenan-induced hyperalgesia in the same monkeys.

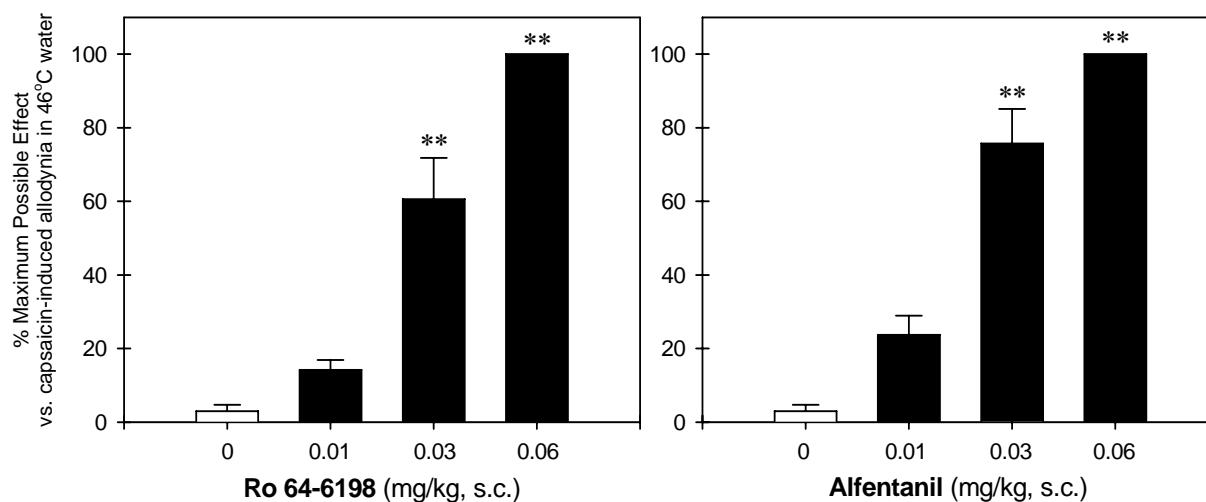


Figure 5. Antinociceptive effects of Ro 64-6198 and alfentanil against capsaicin-induced allodynia in 46°C water. The asterisks represent a significant difference from the vehicle condition (**, $p < 0.01$). Each data point was measured at 15 min after administration of capsaicin.

Figure 5 illustrates the antinociceptive effects of Ro 64-6198 and alfentanil against capsaicin-induced allodynia. Normally, monkeys kept their tails in 46°C water for 20 sec and withdrew their tails within 1-3 sec after capsaicin injection (mean \pm SEM, 1.7 \pm 0.2 sec). Pretreatment with Ro 64-6198 [$F(3,20) = 60.6$; $p < 0.01$] and alfentanil [$F(3,20) = 68.3$; $p < 0.01$] both dose-dependently attenuated allodynia in 46°C water. The ED₅₀ value for Ro 64-6198 dose response (0.024 mg/kg) was similar to that for alfentanil (0.019 mg/kg) under this condition.

More importantly, systemic administration of Ro 64-6198 produced antinociception against capsaicin-induced allodynia in monkeys (figure 5). Capsaicin evokes pain sensation by activating the vanilloid receptor and stimulating the release of

pronociceptive neuropeptides such as substance P from primary afferents (Szallasi et al., 2007). Studies have demonstrated that the vanilloid receptor is required for inflammatory sensitization to noxious stimuli and is essential for tissue injury-induced allodynia and hyperalgesia (Caterina et al., 2000; Davis et al., 2000). Capsaicin-induced allodynia has been used in both monkeys (Ko et al., 1998b; Butelman et al., 2004) and humans (Park et al., 1995; Eisenach et al., 1997) to demonstrate its prominent value for studying pain mechanisms in vivo and pharmacological interventions. Given that capsaicin-sensitive nerve fibers are involved in a variety of nociceptive conditions (Szallasi et al., 2007), effectiveness of Ro 64-6198 for inhibiting capsaicin-induced allodynia indicates that NOP receptor agonists may be effective for treating pain derived from different nociceptive origins.

(As noted, we are currently conducting experiments to study the effects of Ro 64-6198 on carrageenan-induced hyperalgesia in monkeys)

Task 4. Evaluation of potential abuse liability of NOP receptor agonists using the self-administration assay.

- a. Determine and compare reinforcing effects of Ro 64-6198 with those of the mu opioid agonist fentanyl, the psychomotor stimulant cocaine, and the barbiturate anesthetic methohexital in the monkey intravenous self-administration assay to assess whether NOP receptor agonists possess abuse liability.

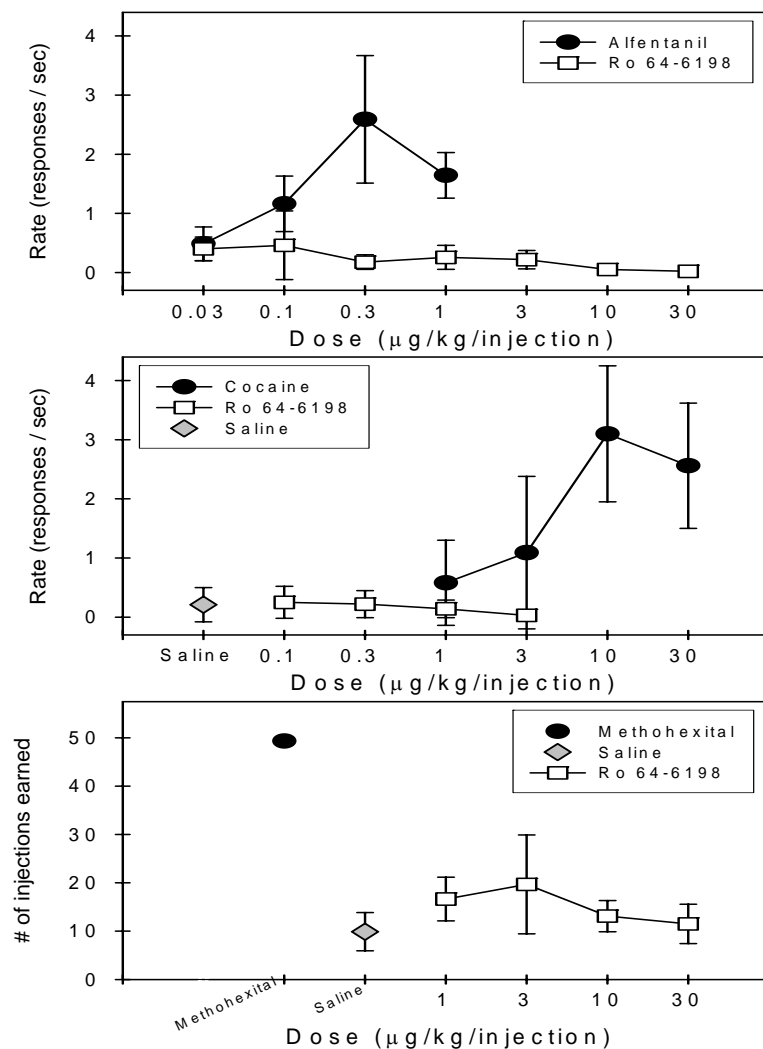


Figure 6. Lack of reinforcing effects of Ro 64-6198 in alfentanil-, cocaine-, and methohexital-maintained monkeys. Top and middle panels: Symbols represent aggregated dose response curves for alfentanil, cocaine, and Ro 64-6198 under a fixed

ratio 30 timeout 45 sec multiple component schedule. Data points are the means \pm SEM for the response rates. Bottom panel: Symbols represent aggregated dose response curves for Ro 64-6198 as compared with responding maintained by a single dose of methohexital 0.1 mg/kg/inj or saline. Data points are the means \pm SEM for the numbers of injection earned.

Figure 6 top panel shows the reinforcing effects of Ro 64-6198 in alfentanil-maintained monkeys. Response rates (responses/sec) for saline, alfentanil, and Ro 64-6198 across a dose range of 0.03 – 30 μ g/kg/inj were assessed. To aggregate data across all subjects, mean response rates engendered by each dose of each drug were averaged. Under this multiple component schedule, contingent saline infusions engendered very low response rates (less than 0.3 responses/sec). The top panel of Figure 6 presents the aggregate dose-response curves for alfentanil and Ro 64-6198. All animals self-administered alfentanil within the dose range tested, generating a biphasic dose-effect curve characteristic of intravenous drug self-administration. In contrast, Ro 64-6198 did not maintain high rates of responding at any of the doses tested, resulting in a flat dose-effect curve indicative of a compound without reinforcing effects under the present conditions. Likewise, the middle panel indicates that Ro 64-6198 did not maintain high rates of responding at doses tested, but all subjects self-administered cocaine, under the same schedule.

Figure 6 bottom panel presents the aggregate dose-response curves for Ro 64-6198 as compared to responding maintained by a reference dose of methohexital or saline. Number of injections earned of Ro 64-6198 across a dose range of 1 – 30 μ g/kg/inj were compared to number of self-injections earned of 0.1 mg/kg/inj methohexital or saline. To aggregate data across all animals, mean number of injections earned by each monkey at each dose were averaged. Methohexital-maintained responding occurred at a high, regular rate across the entire session. When contingent saline was available, animals tended to “sample” early in the session, but behavior generally abated entirely within 15 minutes. No dose of Ro 64-6198 reliably maintained responding above levels observed when saline was available, indicating that Ro 64-6198 had no reinforcing effects under the present conditions.

Taken together, these findings showed a lack of reinforcing effects of Ro 64-6198 in alfentanil-, cocaine-, and methohexital-maintained monkeys (figure 6). The presence of a behavioral effect (i.e., antinociception at 10-30 µg/kg) in the absence of any indication of a reinforcing effect indicates that we have tested sufficiently large doses for reinforcing effects. For example, the antinociceptive doses of intravenous alfentanil were 10-30 µg/kg (Ko et al., 2002), but the doses of alfentanil producing reinforcing effects were 0.1-1 µg/kg (i.e., a 30-100 fold difference in potency) (Winger et al., 1992; Ko et al., 2002). Lack of reinforcing effects by Ro 64-6198 might be expected because several studies have shown that activation of NOP receptors inhibited dopamine release in the striatum and supported the notion that NOP receptor agonists do not have reinforcing or aversive properties of their own (Murphy and Maidment, 1999; Flau et al., 2002). Given that increased dopamine neuronal activity mediates reinforcing effects of several drugs of abuse, we will further study whether NOP receptor agonists can suppress the reinforcing effects of other drugs that have abuse potential in primates.

KEY RESEARCH ACCOMPLISHMENTS

- These results provide a unique functional profile of intrathecal N/OFQ in primates. Unlike the findings in rodents, intrathecal administration of N/OFQ over a wide dose range only produced antinociception. These findings indicate that activation of NOP receptors may have a therapeutic value as spinal analgesics.
- These results provide the first functional evidence that activation of NOP receptors produces antinociception without reinforcing effects in primates. Non-peptidic NOP receptor agonists may have therapeutic value as novel analgesics without abuse liability in humans.

REPORTABLE OUTCOMES

Due to the nature of slow data collection in non-human primates, we only have submitted one abstract for the scientific meeting of American Society for Anesthesiologists (see Appendix). Nevertheless, we expect that 2-3 manuscripts will be published during the 2nd year of this project.

CONCLUSION

Taken together, these experiments demonstrated that (1) intrathecal N/OFQ did not produced hyperalgesia-like effects as reported in rodents, (2) systemic Ro 64-6198 produced antinociceptive effects that are independent from mu opioid receptors, and (3) activation of NOP receptors produced antinociception without reinforcing/abuse liability in monkeys. Ro 64-6198 has only been studied in rodent species (Chiou et al., 2007; Shoblock, 2007). This is the first functional study to investigate the behavioral effects of Ro 64-6198 in primates. More importantly, Ro 64-6198 produces antinociception like alfentanil, a commonly used mu opioid analgesic in the clinic, in two primate nociceptive models, but Ro 64-6198 does not produce reinforcing effects /abuse liability like mu receptor opioid analgesics. These findings may indicate that NOP receptor agonists may be a new generation of novel analgesics without abuse liability.

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APPENDICES

(see attachment)

Behavioral effects of intrathecally administered orphanin FQ in monkeys

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Orphanin FQ (OFQ) is a heptadecapeptide that is an endogenous ligand for the NOP receptor, the fourth member within the opioid receptor family. Pharmacological studies in rodents have shown a dual activity of intrathecally administered OFQ (i.e., both pronociceptive and antinociceptive actions), depending on the dose range, in pain modulation. However, the pharmacological profile of intrathecal OFQ is unknown in primates. The aim of this study was to investigate the effects of intrathecal OFQ over a wide dose range and to compare its effects with ligands known to elicit pronociceptive or antinociceptive effects in monkeys. The nociceptive threshold was measured by a warm water tail-withdrawal assay across different temperatures of water. Intrathecal administration of OFQ (10-100 nmol) dose-dependently produced antinociception against 50°C water. Similarly, a μ opioid receptor agonist, DAMGO (10 nmol), also produced antinociception against 50°C water. Intrathecal administration of OFQ from 1 fmol to 1 nmol did not change the monkey's tail-withdrawal latency in both 46°C and 50°C water. In contrast, intrathecal administration of substance P (100 nmol) elicited pronociceptive effects (i.e., a decreased latency in 46°C water). In addition, when combined with a single dose of intrathecal morphine (50 nmol), intrathecal OFQ (10-100 nmol) dose-dependently produced antinociception against a more noxious stimulus, 54°C water, and it did not attenuate intrathecal morphine-induced itch/scratching responses. Taken together, these results further provided a unique functional profile of intrathecal OFQ in primates. Unlike the findings in rodents, intrathecal administration of OFQ over a wide dose range only produced antinociception. Intrathecal OFQ did not produce anti-morphine actions when it was co-administered with intrathecal morphine. These findings indicate that activation of NOP receptors may have a therapeutic value as spinal analgesics.

(Supported by U.S. Dept of Defense, PRMRP, Grant W81XWH-07-1-0162).

Summary:

Intrathecal orphanin FQ only produced antinociception, not pronociception in monkeys. In addition, intrathecal OFQ in combined with morphine produced profound antinociception. This study further supports the therapeutic potential of NOP receptor agonists as spinal analgesics.